FINDING OF NO SIGNIFICANT IMPACT

FOR

Bacitracin Zinc and Bacitracin Methylene Disalicylate
in Feed for Laying Hens
for
Increased Egg Production and Improved Feed Efficiency

The Food and Drug Administration's Bureau of Veterinary Medicine has carefully considered the potential environmental impacts of these actions and has concluded that these actions will not have a significant effect on the human environment and that an environmental impact statement therefore will not be prepared.

AL Laboratories, Inc. of Englewood Cliffs, N.J. has filed two actions for approval of their use of bacitracin zinc and bacitracin methylene disalicylate (MD) to be incorporated into the feed of laying hens for increased egg production and improved feed efficiency.

The bacitracin MD action is a supplement to the new animal drug application (NADA 46-592), providing for a labeling change resulting in a reduction in the permissible dose range from 10-50 grams/ton to 10-25 grams/ton. Under 21 CFR 25.1(b) this action requires the submission of an EIAR and a submitted EIAR (AL Labs., 1977a) is attached. The bacitracin zinc action is a supplement to the new animal drug application (NADA 98-452), providing for use of a 50 gram-per-pound premix to manufacture complete feeds for laying hens. The EIAR submitted for this action (AL Labs., 1977b) is also attached.

This Finding of No Significant Impact (FONSI) was based primarily upon the environmental information in these EIARs and a review by Feinman and Matheson (1978) on the potential environmental effects of bacitracin (copy also attached).

General

As bacitracin zinc and MD are already being marketed for the uses seeking approval, changes in the introduction, fate, and effects of bacitracin in the environment are not expected. Bacitracin was marketed for these claims under an interim approval pending submission of additional data specified by the NAS/NRC DESI review. These supplements are the result of the new data submitted. These changes in bacitracin use may even result in decreased inputs into and effects upon the environment.

The bacitracins are a group of polypeptide antibiotics produced by Bacillus subtilis and licheniformis. The zinc and methylene disalicylate salts of bacitracin are already used as feed additives to promote growth and for disease control in poultry, swine and cattle. These salts disassociate upon ingestion, releasing the active bacitracin base.

Bacitracin inhibits biosynthesis of bacterial cell walls and is highly active against many species of Gram-positive bacteria and pathogenic Neisseriae. This antibiotic has not significantly influenced Salmonella shedding in chickens fed from 10-100 ppm of bacitracin in their diet, and does not seem to induce bacterial drug resistance.

Physical and Chemical Properties

Bacitracin is composed of amino acids joined in a cyclic polypeptide. The antibiotic is a hygroscopic powder that is stable at room temperature. Bacitracin is reputed to quickly lose antimicrobial activity in aqueous solution at room temperature (AL Labs., NADA 65-280). In contrast to this claim, the Merck Index (1976) says that bacitracin is unstable in alkaline solutions, but stable in acid solutions. Bacitracin MD and Bacitracin zinc are soluble in water to the extent of 50 mg/mℓ and 5.1 mg/mℓ respectively (Merck Index, 1976; Weiss et al., 1957). Both are practically insoluble in ether and chloroform. No lipid-water partition coefficients are available; however, the coefficient should be low, based upon the high water solubility of the drug.

Manufacturing Introductions

The manufacturing process includes the production of the antibiotic through fermentation and the manufacture of the premixes. Most of the fermentation processing occurs in Norway and meets their pollution control requirements. The manufacturing processes occurring in the United States meets all local, state, and federal consideretions regarding protection of the environment.

Industrial wastewaters are discharged to a municipal sewage system for handling in the treatment facility. Drying and packaging of the products are done under appropriate dust control systems. A sanitary landfill is used to dispose of the solid wastes. We conclude that the manufacture of the bacitracin MD and zinc does not appear to have a significant impact on the quality of the environment when produced according to the procedures described in the applications.

Introduction into Environment through Excretion by Target Animals

Experiments with chickens, dogs, and swine demonstrate that animals given bacitracin orally absorb little of the antibiotic and bacitracin is excreted essentially intact in their feces. Due to this poor absorption, bacitracin, even at levels exceeding recommended dosages, does not produce detectable residues in animal tissues.

Chickens fed 11 ppm zinc bacitracin contained 31 to 54 ppm (wet weight) in their intestines, (Bare et al., 1965), while litter from facilities where chickens were continuously fed bacitracin contained from 0.05 to 8.5 ppm (Webb and Fontenot, 1975).

As most laying hens are kept enclosed and their excreta is allowed to accumulate undisturbed in these enclosures for periods of time of up

to a year (White and Forster, 1978), and bacitracin appears to degrade rapidly in water, excreta, and soil (see following), it is expected that bacitracin introduction into the environment via laying hen excreta will be minimal.

Fate in the Environment

Persistence and Degradation

The types, quantities, and bioactivity of bacitracin metabolites present in the excreta of target animals are not determined in any studies reviewed by the Agency. We believe that the polypeptide chemical structure, absence of hard-to-degrade chemical substituents (such as halogens) and high water solubility suggest that bacitracin is biodegradable, probably by successive deamination and dealkylation reactions catalyzed by enzymes present in most soil bacteria and fungi.

Bacitracin excreted in feces has been found to be unstable when incorporated into soil. An environmental half-life of 10 days or less was observed for zinc bacitracin when exposed to normal environmental soil conditions of moisture, temperature, and pH (IMC, 1977).

Bacitracin inactivation has been examined in excreta from broiler chickens continuously fed mash containing 500 g bacitracin MD per ton of feed (AL Laboratories, 1977a and b). Fresh excreta contained 6.17 ppm (dry weight basis) of bacitracin. This was reduced to 1.3 ppm in excreta held at room temperature for seven days and the half life was estimated to be between four and seven days.

Mobility in the Environment

Pinck, Holton and Allison (1951) demonstrated bacitracin to be one of a group of amphoteric antibiotics which are weakly adsorbed and easily released in active form from clay-antibiotic complexes that would occur in soils. This antibiotic was released from all soil types and clays tested. Based on these data and the high water solubility of bacitracin, we conclude that this antibiotic is mobile in soils, with temporary or partial retention occurring depending on soil pH, clay composition and content.

Bioaccumulation in Target Animals

No tissue residues of bacitracin have been found in chickens, turkeys, or laying hens consuming feed containing bacitracin at as much as 1000 g/ton (1100 ppm) until the day of sacrifice. No detectable residues have been found in tissues of cattle or swine consuming bacitracin MD at 500 g/ton (550 ppm) (AL Laboratories, 1977a and b).

Since bacitracin has high solubility in water and low solubility in organic compounds (properties favoring efficient excretion), has poor absorption in target animals and is inactivated in animal wastes and

soils we conclude that it is unlikely that long term bioaccumulation would occur with environmental residues of bacitracin.

Environmental Effects

Quantities of bacitracin required for induction of oral acute toxicity among rabbits were found to be more than 5200 mg/kg body weight (Payne et al., 1951). In acute toxicity studies with mice, the oral LD_{50} was found to be 3375 mg/kg body weight (Bacharach et al., 1959).

When bacitracin was fed to chickens at 300 mg/kg of feed for 90 days, there were no toxic effects; however, bacitracin at 1000 mg/kg of feed led to slight effects on the kidney tubules (Simeonov et al., 1975). Bacitracin is not used parenterally in animals because of potential nephrotoxicity. Lethal doses produce renal tubular damage.

Bacitracin-related phytotoxicity was not observed in the limited data available. Bacitracin from the excreta of medicated target animals did not affect yield in potted oats (Tietjen, 1975).

We believe that bacitracin probably has no effect upon the Gram-negative free-living nitrogen fixers (Azotobacter) or symbiotic nitrogen fixers (Rhizobium) or upon the nitrate and sulfate oxidizing organisms (Nitrosomonas, Nitrobacter, Thiobacillus) since it acts mainly upon Gram-positive organisms and Gram-negative cocci. However, there are no specific data to confirm this speculation.

The short environmental persistence of bacitracin bioactivity precludes long-term toxic effects frc environmental residues, in any event.

Conclusion:

Given the following, the potential for adverse environmental effects due to the use of either bacitracin zinc or MD in laying hens seems minor.

1. Bacitracin appears to be relatively non-toxic.
2. Bacitracin seems to be rapidly inactivated in water, animal excreta, and soil.
3. Laying hens are uniformly confined and their excreta is also usually confined for periods of time that would allow extensive degradation of bacitracin residues to occur.

In addition, as bacitracin is already being marketed for the uses seeking approval, the proposed actions may not add to the environmental introductions of bacitracin and do not appear to result in increases in the environmental costs associated with the use of the drug.

A more detailed evaluation of all uses of bacitracin in all species for which it is approved (poultry, swine and cattle) is desirable, however. The following information is needed and will be requested from AL Labs. Initially a literature search should be performed to determine information already extant.

1) Additional information on the physical-chemical properties of bacitracin zinc and bacitracin MD respectively.

   a) Octanol-water partitioning coefficient

   b) Vapor pressure

   c) UV-visible adsorption spectra

2) Additional information on the observed inactivation of bacitracin antimicrobial activity

   a) The probable pathway and rate of degradation of the bacitracin molecule

   b) Processes involved in degradation (e.g., chemical, photochemical, and/or biological)

3) Ecological effects data

   a) Antimicrobial spectrum of activity, particularly for non-pathogenic, beneficial bacteria.

   b) Other effects, as determined from the information gathered above.

4) Manufacturing data

   a) An update on the specific locations where the respective bacitracins are manufactured.

   b) An update on the certifications that relate to meeting the local, state, and Federal considerations regarding protection of the environment.

Summary

The proposed actions are sufficiently limited in scope that they do not appear to result in a significant increase in the potential for manufacture and use of the drug that could result in adverse environmental impacts. However, there are sufficient gaps in our actual knowledge of environmental introduction, fate and effects of bacitracin to strongly suggest that additional data are needed in order to evaluate the total environmental effects that may occur from the combination of all uses currently allowed. The Bureau of Veterinary

Medicine is taking steps to obtain the additional data needed.

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Attachments:

Environmental Impact Analysis Report
Draft Environmental Impact Statement: Subtherapeutic Antibacterial Agents in Animal Feeds, pp. A-70--A-75

Copy to: Hearing Clerk
Orig, Dup, HFV-16
HFV-1
HFV-102
HFV-9
Branch File, HFV-147